EXHIBIT 3

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(Pause.)
THE WITNESS: I don't believe that that is specified.
BY MR. PARKER:
Q. If you would, please turn to -- let me see if I can find it.
A. By the way, can we go back to where you asked about steroids?
Q. Yes, sir.
A. I would just point out that any patient who makes it to Columbia for seronegative villous atrophy who has not responded to a gluten-free diet, steroids would be a fairly logical step in their management; and for more or less any inflammatory disorder, there is going to be some clinical improvement on either a steroid or an immunosuppressive medication, so I think that -- that could be true and it doesn't have any impact on my belief that olmesartan was causing their syndrome.
MR. PARKER: Move to strike.
BY MR. PARKER:

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Q. Doctor, what you just said is not accurate, however, with regard to the Mayo series of 22 patients who reported not to have responded to steroids; correct?
MR. SLATER: Objection; foundation.
You can answer.
THE WITNESS: I think it depends on -- I don't know how each group responded -- how each group defined response; and even if there was a difference in the response, even if you defined it the same way, I would say that there's variation in the disease presentation and the disease process.
And so if some patients did -- I would expect most patients to respond to some extent; but if some didn't, that doesn't really affect my thinking.
BY MR. PARKER:

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Q. But my question was more pointed. The Mayo Clinic is also highly regarded as a referral center for small bowel disorders, including celiac disease.
A. Yes.
Q. Correct?
A. Uh-hum.
Q. And we can pull it out later, but is it your understanding that what they reported about those 22 people is that they did not respond to immunosuppressants?
MR. SLATER: Objection.
You can answer.
THE WITNESS: I really wouldn't answer that without looking at the paper and that -- I'd like to look at the paper before I say --
MR. PARKER: Let's work through this one, then I promise you we will look at the Mayo paper.

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BY MR. PARKER:
Q. With respect to this paper, however, what we're told is that all of these patients were referred to Columbia with a diagnosis of refractory celiac disease; correct?
A. That sounds quite reasonable, but let me verify that. Could you tell me where you're finding that statement?
Q. Give me one second.
A. Sure.
Q. Under results, the second page?
A. Okay.
Q. You'll see the second sentence, "All patients had been referred with a diagnosis of poorly responsive/refractory CD." That's celiac disease?
A. Uh-hum.
Q. So can we agree that all 72 patients had come to Columbia with a diagnosis of their treating doctors with

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either poorly responsive and/or refractory celiac disease?
A. I would accept that statement with a proviso, which is, the sentence preceding it states that these were patients with seronegative villous atrophy, so that means that these patients had been serologically tested for and found to be negative for the test of celiac disease.
Q. But there is a clinical entity of seronegative celiac disease, is there not?
A. There is.
Q. Okay. So these patients were tested to have -- not to have the antibodies typically seen in celiac disease patients, but nevertheless were thought by their physicians who referred them to Columbia to have celiac disease according to what your colleagues wrote here.
MR. SLATER: Objection.
You can answer.

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THE WITNESS: They were thought to have a variation, a rare, complicated form of celiac disease, yes.
BY MR. PARKER:
Q. Thank you.
If you would flip over three pages under the discussion section, which is the middle column --
A. Yep.
Q. -- perhaps you can explain this to me: Down towards the first paragraph, do you see where it begins "An interesting finding"?
A. Uh-hum.
Q. -- An interesting finding in our series was the number of patients who were initially labeled with unclassified sprue who were ultimately found to have villous atrophy as a result of olmesartan use.
I managed to read that correctly, did I not?
A. You did.

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Q. I'm puzzled by the word who were initially found -- initially labeled with unclassified sprue. We just got done reading where they came to your -- Columbia, not your -- center with refractory celiac disease. Is that the same or different than unclassified sprue?
MR. SLATER: Objection.
You can answer.
THE WITNESS: I think the problem here is that you're -- we're a bit conflating what the outside physicians thought, which -- with what was thought at Columbia.
So the outside physicians said, okay, you've got seronegative refractory nonresponsive celiac disease. And from my interpretation of this statement -- and I'll acknowledge that there's a little bit of vagary here -- these are patients

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who at Columbia were classified as having unclassified sprue until the publication of Rubio-Tapia and then were instead classified as olmesartan enteropathy.
MR. PARKER: Fair enough.
BY MR. PARKER:
Q. So the process as you understand it were, patients came in with a label of refractory celiac disease. They got looked at, worked up by your colleagues. A number of them were told --
A. Seronegative refractory celiac disease.
Q. Seronegative refractory celiac disease.
A. I'm not making that point to be a jerk. I'm making that point because both of these are rare manifestations of celiac disease and not specifically related, so I'm saying that these patients were thought to have two concomitant uncommon variations of celiac

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disease.
Q. Fair enough. And when they came to Columbia initially, they were sent home, some number of them, with a diagnosis of unclassified sprue.
A. I would agree with the interpretation that you just made.
Q. And when the label was changed from seronegative refractory celiac disease to unclassified sprue, would they have been told, you can go home and start eating gluten because you don't have celiac disease?
MR. SLATER: Objection.
You can answer.
THE WITNESS: I'm afraid I can't really answer that question.
MR. PARKER: That's all you can do for me. Okay.
BY MR. PARKER:
Q. Now let's go to table number 3.
A. Table 3, sure.
Q. And you'll see on the

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right-hand side of that column, there's a column labeled "IS"?
A. Uh-hum.
Q. And that would have been immunosuppressants?
A. Yes.
Q. Would that have been a drug indicated for patients diagnosed with unclassified sprue?
A. This would be a drug that you would use for any patient with an inflammatory disorder that you couldn't get under control in a less -- this is a -- we would consider this sort of a big-gun drug to introduce to a patient so that you would -- you would introduce it when other less potentially toxic treatments had failed.
Q. And we're told that all 16 of these patients had -- let me get the exact words -- symptomatic improvement; is that correct?
A. Can you tell me where you read those words?

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Q. Do you see the positive signs under the IS --
A. Oh, yes.
Q. -- I think that's what I was looking at. Would that not indicate improvement on immunosuppressants?
A. As I stated before, any inflammatory disease likely to have some improvement on immunosuppressant. So, yes, the interpretation of plus sign under IS, or clinical improvement slash IS, that indicates that they had some improvement.
And the following -- the following column indicates that each and every case relapsed after stopping the immunosuppressants.
Q. So that we understand -- and is this reflecting the clinical course of these patients after they came back to Columbia when they were contacted and then sent back home? Is my question clear to you what I'm asking?
A. Maybe you could say it in a

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different way.
Q. Sure. You've described that after learning about what the folks in the Mayo were going to publish, there was an effort to reach out to these 16 patients who were found to be taking olmesartan and who had been diagnosed with seronegative celiac disease, refractory celiac disease; correct?
A. Yes.
Q. And there was some effort to talk to them and get -- and reconnect with them, and they found 16 patients who had been taking olmesartan; correct so far?
A. Yes.
Q. And some of those patients came back for further medical follow-up, including some had rebiopsies; correct?
A. Uh-hum.
Q. Yes?
A. Yes.
Q. And they were instructed to stop taking olmesartan.

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A. To the best of my knowledge.
Q. What I'm trying to discern right now is, when did these 16 patients have their clinical improvements when they were given immunosuppressants and then have relapse when they stopped taking their immunosuppressants? Was it the same time they were told to stop taking olmesartan?
A. Don't know the answer.
Q. Okay. Who would we talk to who would know that?
A. I would speak to Dr. Green. He's the senior author of the paper.
Q. Was he the one running the study? I mean, sometimes senior authors are just senior authors.
A. I wouldn't -- I wouldn't speculate as to how --
Q. Okay. Fair enough. Okay.
Let me put that aside and come back to what I want to discuss before we get visited by lunch.
A. Sure.

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Q. Doctor, I want to ask you to put aside the plaintiffs, whether disclosed or undisclosed, that you've been asked by counsel to look at, their specimens.
Can you give me some idea in your world as a practicing pathologist how many reports you've generated in which you've concluded in words to the effect that the conditions I see in this patient are consistent with someone taking olmesartan?
MR. SLATER: Objection.
You can answer.
THE WITNESS: May I refer to my -- to the report?
MR. PARKER: Please. You can always refer to anything you want to look at, Doctor.
THE WITNESS: Okay. Let us look at page -- at the bottom of the first paragraph, the rather long paragraph --
BY MR. PARKER:

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Q. Page what, sir?
A. Oh, sorry. Page 4.
Q. Okay.
A. -- here, you'll see phraseology that I employ fairly frequently. To put an exact number on how many times I've said this, I couldn't, but I would say perhaps dozens of times.
So if I have a case in which I see the findings described here in the report and I don't know whether the patient is taking olmesartan, is taking -- has had celiac testing, has had some bone marrow transplant -- if I don't have a complete clinical picture, I give a differential diagnosis, an example of which is provided here.
If you're asking in how many cases have I had the clinical data and we have come to the conclusion that olmesartan is the most likely culprit, I wouldn't be able to put an exact number on it, but not counting the cases that

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I've seen through my work with Mr. Slater, you know, more than 10 and less than 25 seems to be in the ballpark.
Q. And on cases that come to you in your day-to-day job, not as a litigation consultant, have you ever concluded and written in a medical report, this patient has sprue-like enteropathy associated with olmesartan or olmesartan-associated enteropathy or some variation of that term? Have you said this patient has it as opposed to saying this is consistent with that?
A. I don't think that I would ever use those specific words. I think that those specific words imply a level of clinical detail that rarely is available to pathologists at the time of signing out a case.
When I've encountered these cases, I've given descriptive diagnoses, like I describe here. I've listed plausible items on the differential diagnosis, which certainly have included

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olmesartan on a number of occasions, many perhaps, and I attempt to follow up that diagnosis with a conversation with the clinician.

If it's a patient being seen at our Celiac Disease Center, it's very likely that that patient would then be presented in an interdisciplinary conference where the gastroenterologists and myself and other pathologists would discuss the case and we could come to that conclusion.

But the words written on a -- you know, on a pathology report, this is and can only be olmesartan enteropathy, that phraseology is unlikely to make it to a pathology report.

Q. In fairness to my question, I didn't say "and can only be."

A. Okay.

Q. All right? I just want to make sure you're not hedging on me. My question is, have you ever said in a pathology medical record, this is a case

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of olmesartan-associated enteropathy or sprue-like enteropathy?

MR. SLATER: Objection; asked and answered. I mean, he just went through this in detail with you.

MR. PARKER: He just hedged and said --

MR. SLATER: He didn't hedge at all. Come on, Bruce.

MR. PARKER: Doctor, can you answer my question?

THE WITNESS: I'm sure that I've said that I suspected or this -- you know, this should be considered clinically. That's about -- that's probably the strongest phraseology that I would use in this condition.

MR. PARKER: Thank you. We'll have some lunch.

(A luncheon recess was taken from 12:36 p.m. to 1:18 p.m.)

BY MR. PARKER:

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Q. Doctor, we're back on the record after our lunch break and I want to talk to you for a moment about a clinical entity we started to talk about before lunch in connection with the -- how do you pronounce it -- DeGaetani -- paper of unclassified sprue.

A. Uh-hum.

Q. Are the terms unclassified sprue and idiopathic enteropathy synonymous?

A. Idiopathic enteropathy is not a term that I use frequently in my practice or encounter too frequently in the literature. Unclassified sprue is saying someone has a sprue-like illness and we don't know what the possible etiology is, as opposed to, say, celiac sprue or olmesartan enteropathy or one of these other sprues where we believe we know the cause.

So idiopathic enteropathy -- is that term that you used?

Q. Yes.

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A. -- you know, that to me doesn't refer to any specific entity. That would be a descriptive term that if you used that term in discussion with me, I would take it to mean something similar to unclassified sprue.

Q. Okay. Well, if you're more comfortable with unclassified sprue, I'll use that term for my next area of questions.

A. Okay.

Q. Doctor, people today continue to get the label of unclassified sprue; correct?

A. Yes.

Q. And I can -- can I presume correctly that before Benicar, olmesartan was available in 2002 and people received the diagnosis of unclassified sprue?

A. Uh-hum.

Q. Yes?

A. Yes.

Q. As you just explained, doctors diagnose someone with

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unclassified sprue when they present with symptoms of enteropathy for which there's no known cause at that point in time.

A. Yes.

Q. And for all such people, there is some biological reason for them developing sprue. Medical scientists simply haven't identified what it is.

MR. SLATER: Objection.

You can answer.

THE WITNESS: I think that what you just said is plausible. I would expand on that just a little bit to say that to call someone an unclassified sprue patient means, as you described, we don't know what the cause of their sprue is.

It doesn't -- it could mean -- that could come from one of two reasons: Either they have a sprue which has a novel cause that we don't know or they have sprue due to a common cause and we have not

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been able to make the diagnosis for whatever reason, so there are two different ways to get at that diagnosis.

BY MR. PARKER:

Q. In someone who is diagnosed with unclassified sprue and then starts taking olmesartan, there's no reason -- well, let me rephrase the question.

For whatever reasons one may develop an unclassified sprue, there's no biologic reason they can't have that and take olmesartan at the same time and be wholly unrelated to each other.

MR. SLATER: Objection.

You can answer.

MR. PARKER: Do you agree?

THE WITNESS: I'd like to ask you to clarify the question, if I may. Are we talking about a hypothetical situation in which a patient has signs and symptoms of sprue, has a biopsy that shows sprue-like changes, and God

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himself has come to the deposition room and said this patient has never touched olmesartan before this developed and then started taking olmesartan after that? Is that the situation that you're describing?

MR. PARKER: Well, I didn't invoke God, but I'll make the question easier for you.

BY MR. PARKER:

Q. Is someone is diagnosed with unclassified sprue who has never taken -- and let's just say his doctors say so and patients say so -- never taken olmesartan, they can continue to have unclassified sprue notwithstanding the fact that they're now taking olmesartan.

A. I think that's a possible, although quite rare, scenario, but I do concede that that is a possible scenario. I would also just add to that, we don't know in those patients if olmesartan could contribute or make -- or exacerbate

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their sprue. For instance, we don't know in -- there are patients who have -- just based on epidemiology, there are certainly patients who have true celiac disease and who have been prescribed olmesartan. We don't know if the olmesartan affects those patients differently than patients without celiac disease.

Q. And there's no literature to suggest that it does.

MR. SLATER: Objection.

You can answer.

THE WITNESS: Or doesn't.

MR. PARKER: Let's talk about the affirmative. Nobody's published a paper of any type positing or proposing that a patient with celiac disease is made worse if they start on olmesartan.

MR. SLATER: Objection.

You can answer.

THE WITNESS: There's

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nothing in the published literature to that effect yet.
BY MR. PARKER:
Q. Now, going back to my question about unclassified sprue, it is reported in the literature that patients who have unclassified sprue, some number of them spontaneously resolve.
Have you seen that in the literature?
A. That sounds familiar, but before I agree to that point, I'd like to -- if you have something with you that documents that, I'd like to confirm that.
Q. Sure, sure.
Have you ever seen that in your clinical practice, of patients with diagnosed unclassified sprue resolving spontaneously, or has it been reported to you by your colleagues in the GI section?
A. And for the purposes of this question, we're excluding the cases seen at Columbia who were thought to be unclassified and later categorized as

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olmesartan?
Q. Yes, I'm not involving olmesartan at all.
A. Okay. I don't remember a case, but I don't think it sounds unreasonable.
- - -
(Deposition Exhibit No. Lagana-6, 2016 Original Article "The clinical and phenotypical assessment of seronegative villous atrophy; a prospective UK centre experience evaluating 200 adult cases over a 15-year period (2000-2015)" by Aziz, et al, was marked for identification.)
- - -
BY MR. PARKER:
Q. Doctor, Exhibit 6 is a copy of the study by Drs. Aziz and others, which your colleague, Peter Green, is a co-author on.
Do you see that?
A. Yep.

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Q. And this is one of the papers that was listed in that supplemental reliance list that we marked earlier today?
A. Uh-hum.
Q. Okay?
A. Yes.
Q. And it is not one that is referenced in any manner in your report; correct?
A. That's correct.
Q. Have you read this paper before coming to the deposition today?
A. I have.
Q. It is a -- it was, as described, a prospective study over, what, 15 years, 10-plus years?
A. It looks like 15 years.
Q. Okay. And it was an attempt by these investigators to collect cases, as we discussed previously, of seronegative villous atrophy?
A. Yes.
Q. And in this report, they

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describe various causes that they attribute to these patients, which are reflected in figure number 2, the pie chart?
A. Figure 2. Okay.
Q. Do you see that, Doctor?
A. I do.
Q. And they specifically asked a question to themselves as they reviewed these cases of whether the patients had been exposed to any form of an ARB; is that right?
A. I believe I recall reading about that.
Q. And if you look at the pie chart, they report in this group of 200 that there were 13 that they concluded had a drug-induced seronegative villous atrophy?
A. I see that.
Q. And then there was a group of 36, or 18 percent, that they describe as idiopathic. Do you see that down below as well?

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A. I do.
Q. And if you look on page 5, Doctor, the same page as the pie chart -- excuse me -- on the right-hand column, do you see the paragraph beginning, "Finally, in 36 cases"?
A. Uh-hum.
Q. And I'm going to paraphrase, but you tell me if I misstate this, what they're saying. They looked at these 36 cases of seronegative nonceliac disease and report that they were unable to attribute any cause after looking for drug induced reasons; and they report that 26, or 72 percent, had spontaneous recovery by evidence of duodenal biopsy?
A. I see that, yep.
Q. Is this then an example in the literature of patients -- they used the term "idiopathic enteropathy" -- as we discussed, people with enteropathy of unknown causes, medications being considered, that resolved spontaneously?
A. That is what this group

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reports, so I would agree that this group has reported some examples of that. I would add that this is made after the exclusion of a drug-induced enteropathy --
Q. Yes, sir.
A. -- so that really is a different group of patients than the olmesartan enteropathy patients who are diagnosed, in large part, based on their response to cessation of the drug.
Q. My question, however, is that what this is reporting is that people who have unclassified sprue or idiopathic enteropathy, those conditions of unknown causes do resolve -- some number of them do resolve -- spontaneously.
A. According to this case series, this is -- this case series has shown some examples of that.
Q. And when you -- can you give me some idea when this paper was brought to your attention and you read this

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paper?
A. I think that -- I think that perhaps this came to my attention either through the defense expert reports or from Mr. Slater. I don't recall precisely.
Q. But relatively recently --
A. Relatively recently, yeah.
Q. When you did have it brought to your attention in one of those two ways and you saw that your senior colleague, Peter Green, was an author, have you ever walked down to his office and asked him about this paper?
A. I have not spoken to him about this paper.
Q. Have you ever had a conversation with Peter Green or some of the other senior gastroenterologists about spontaneous remission of unclassified sprue?
A. You know, I can't recall a specific instance.
Q. Doctor, putting aside the

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history of olmesartan, what clinical features as reported in the literature or through your training of unclassified sprue are different in any respects to sprue-like enteropathy associated with olmesartan?
A. The main differences would be exposure to olmesartan and improvement upon cessation of olmesartan.
Q. But my question was the clinical features of it.
A. Well --
MR. SLATER: Objection. This is -- are you going back over this? Unless I'm misunderstanding. Didn't we go over this --
MR. PARKER: Not of unclassified sprue, no.
MR. SLATER: Oh, unclassified sprue.
MR. PARKER: Yes.
MR. SLATER: Okay.
THE WITNESS: Again, in

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unclassified sprue, you can see a range of findings similar to what we discussed with olmesartan enteropathy. And I can't -- you're asking if there's a specific clinical feature that's different in one versus the other?

MR. PARKER: Yes, I'm -- yes.

THE WITNESS: Okay. Simply the history of olmesartan exposure.

BY MR. PARKER:

Q. Okay. Put aside whether the person used drug. In their symptoms, their clinical -- I mean their findings, when you take their blood, when you do all the stuff that doctors do to someone, is there anything that you can say, you know, that happens with people with unclassified sprue, it doesn't happen with olmesartan or vice versa?

MR. SLATER: Objection. You can answer.

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THE WITNESS: I don't believe so.

BY MR. PARKER:

Q. Doctor, have you ever had a discussion with your colleagues at Columbia on the following issue: Have you ever been a participant in discussion that's asked the question, in someone -- how do we know in someone who has unclassified sprue and who happens to be taking olmesartan that it is the olmesartan cessation that is a result of them getting better rather than spontaneous remission of the unclassified sprue?

A. Well, in some cases, these patients have suffered for years and the cessation of olmesartan on a time scale, although sometimes it can take awhile to heal, often these patients feel better even within days.

So it would seem unlikely that in a bunch of patients with somewhat variable, but some similarities in their

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presentation, all with the same drug exposure, that the intervention of removing the drug would cause spontaneous resolution of a totally unrelated condition so consistently.

So I think that -- and of course there are rechallenges, there are rechallenges in the literature. I reviewed a number of cases in which patients were rechallenged and the symptoms returned, quickly in a lot of cases.

So I think that, you know, we are making determinations to a reasonable degree of medical certainty, but I would think beyond that, the idea that all -- that all or most of these patients had unclassified sprue and just happened to get better totally unrelated to the cessation of olmesartan, that's, you know, astronomical. The odds against that are astronomical.

Q. But that wasn't my question. My question was, have you ever had that

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discussion with your colleagues as to how can we determine whether or not in a given patient -- if they happen to get better some period of time after we discontinue olmesartan, how can we be sure that the olmesartan was the reason as opposed to a spontaneous resolution of the symptoms? Have you had the discussion, is all I'm asking.

A. We've had the discussion in relation to individual patients. I don't think that we've had it -- you know, I don't remember anyone pounding the table and saying, no, no, this is unrelated. How could you prove to me that -- the change was so dramatic in these patients, as they report, based on the cessation of the drug, that there wasn't really much pushback against that explanation. But it was certainly discussed.

Q. And the Aziz paper is not the only paper in the literature that talks about unclassified sprue or idiopathic enteropathy patients resolving

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spontaneously, is it?
A. I would certainly presume not, but as we said before, I would like to see the specific examples that you're referring to.
Q. Why don't you pull out your supplemental reliance list, sir, please.
A. Okay.
Q. You have it -- I'm sorry. It should be Exhibit 4?
A. Okay.
Q. Here (Indicating) it is.
A. Okay.
Q. Is there one on your supplemental reliance list that talks about spontaneous resolution of unclassified sprue?
MR. SLATER: Is the question whether that's the title of the article?
MR. PARKER: No. Does one of these papers address that topic?
MR. SLATER: Objection.

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THE WITNESS: I think that if there's a paper in mind that you'd like me to look at, I'm happy to do so. If you're asking me to remember the detail -- you know, whether that detail was included in any of these, I think that's a bit -- I would not venture a guess in that regard.
MR. PARKER: Okay. And I don't want you to guess.
THE WITNESS: Okay.
- - -
(Deposition Exhibit No. Lagana-7, 2015 Paper "Self-limited coeliac-like enteropathy: a series of 18 cases highlighting another coeliac disease mimic" by Brown, et al, was marked for identification.)
- - -
BY MR. PARKER:
Q. Let me hand you Exhibit No. 7.

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A. Okay.
Q. And this is a paper on your supplemental reliance list; correct?
A. Yes.
Q. Can I assume that since it's on your reliance list, that you've read it?
A. I have read it.
Q. And would this have been one that came to you relatively recently, like the Aziz study?
A. Sorry. What's that?
Q. Like the Aziz study.
A. I saw this several months ago. Yeah, I -- I believe I -- Histopathology is one of the journals that I get Table of Contents e-mailed to me every month, so I believe I saw this when it came out and I looked at it again in preparation for the deposition.
Q. Okay.
It was not studied, however, for purposes of writing your general causation report.

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A. Correct.
Q. Okay. Now, this is a paper -- and this is a pretty good journal, is it not?
A. I agree.
Q. I assume you wouldn't waste your time reading bad journals. Right?
A. I have published in Histopathology. I think it's a good journal.
Q. Very good. Okay.
And this is describing a series of 18 people who have, as described here, enteropathy that looks like celiac, but is not celiac.
A. Correct.
Q. And is that deserving of the moniker of unclassified sprue or idiopathic enteropathy or is this yet another label that we have to put on a clinical syndrome?
MR. SLATER: As opposed to what they called it here?
MR. PARKER: As opposed to

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what they called it.
THE WITNESS: Yeah, I mean, I don't think that they expressly labeled these patients as unclassified sprue unless -- perhaps if you recall that they did, I'm open to reconsidering that statement, but I don't remember them labeling them in that way.
This paper -- you know, this is a study that was done in Australia and it looks like 66 percent of their patients were thought to be infectious. The infections that they encounter in Australia could certainly be different than the infections that we encounter here.
I mean, I -- I acknowledge this paper. I don't dispute their -- the generalities of it. I would probably leave my assessment at that, unless you'd like to talk

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about it more.
MR. PARKER: I'm not sure that was my question.
BY MR. PARKER:
Q. But my question now is, as you read this paper, the clinical condition that's being described, is it describing an unclass -- a patient population of unclassified sprue?
MR. SLATER: Objection.
You can answer.
THE WITNESS: Okay. I would need to refresh myself.
MR. PARKER: Take a look at it, please.
THE WITNESS: Okay.
(Pause.)
THE WITNESS: Well, to diagnose someone with a sprue-like illness, I would want to see some chronicity to it. Here, they describe that all of the cases had abrupt onset of symptoms and they don't describe for how long the

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symptoms lasted, unless you found that someplace which I haven't seen it.
So I would say that there is some similarity here to a sprue-like illness, but I don't think that they're exactly the same.
BY MR. PARKER:
Q. Have you ever seen a patient that is described in this report?
MR. SLATER: You mean are any of these his patient?
MR. PARKER: No. Have you ever seen a patient with these type of symptoms in his clinical practice.
MR. SLATER: Objection.
You can answer.
THE WITNESS: I have seen patients with acute onset of symptoms and with histology that looks like this. I don't -- I don't recall any in which I had

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the extent of clinical information that they had here, so I couldn't say if I have seen patients that, you know, fall entirely within the spectrum of what they're reporting here.
BY MR. PARKER:
Q. And in an effort to try to understand why these patients had this clinical presentation, they describe a number of different reasons, one of which are medication -- medication-associated enteropathies, including olmesartan.
MR. SLATER: Objection. That's -- foundation, actually. There's an issue with what you just said.
But you can go ahead.
THE WITNESS: Sorry. I can answer?
MR. SLATER: You can answer.
THE WITNESS: Okay. Yes.
BY MR. PARKER:
Q. And after ruling those

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out -- and they did according to them rule those out; correct?
A. Yep.
Q. -- they were left with 18 patients, 10 of whom were said to have resolution of all their symptoms within one month of the onset. I'm sorry. That's under results (Indicating).
A. Most within two weeks -- okay. Yes, I see that now.
Q. Putting aside whether you would fit these people into the rubric of unclassified sprue or something else, here we have yet another grouping of patients with small bowel symptoms who are said to have resolved spontaneously.
A. With a different set of symptom -- symptoms that last two weeks are different than symptoms that last two months or two years, so I would actually think -- now that I've seen that bit of data in the results, that makes me feel like these patients are less like our olmesartan enteropathy patients than --

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they're very different patients.
And the other thing I noted when I looked at this is that some of these are pediatric patients. We have a patient that's 2, a patient who's 9, a number of patients in their 30's, their 20's.
So this really to me is a different set of patients on a different continent with different exposures to viral pathogens, bacterial pathogens. If you're asking me will I grant the broad point that some patients who have villous atrophy and inflammation on biopsy can resolve on their own, yes, I grant that point.
I think that this is a very different set of patients, though, than the ones that we're talking about in the group of olmesartan --
Q. I was simply trying to respond to your invitation that I share with you other information about enteropathies that resolved

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spontaneously. That's all.
A. I appreciate it and --
Q. Okay.
Has this discussion jogged your memory of any other papers that you've read in the literature of enteropathies not associated with medications that resolved spontaneously?
A. I'd like to just take a bit of -- to clarify your language a little bit. You said any other enteropathies that resolved spontaneously. These patients in the Brown paper, I don't classify as -- as an unclassified sprue patient or -- this is a different cohort of patients. I just want to -- in my opinion, this is a much different cohort of patients. I don't put them in the same category as, say, the DeGaetani paper.
MR. PARKER: Okay. I move to strike.
BY MR. PARKER:
Q. That wasn't my question. My

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question was enteropathy. I used that term.
You're not going to fuss with me that these people don't have enteropathies, are you?
MR. SLATER: Objection to the form.
You can answer.
THE WITNESS: If we're defining enteropathy just as inflammation and changes to the villi with no -- without taking into account any clinical variables, then I'll not fuss with you about that.
MR. PARKER: I was using your definition. That's why I asked you that at the outset of the deposition.
THE WITNESS: Well, I used a broad --
MR. SLATER: Okay. One second.
Objection. He didn't ask a

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question. All he did was make a statement to you.
BY MR. PARKER:
Q. As you defined enteropathy at the beginning of this deposition, these people have enteropathies.
MR. SLATER: Objection.
You can answer.
THE WITNESS: Can I have it read back to me?
MR. PARKER: From four hours ago, I don't think we're going to spend the time, so I'll move on if you don't remember your definition.
THE WITNESS: Okay.
MR. PARKER: Okay.
- - -
(Deposition Exhibit No. Lagana-8, 2012 Original Article "Severe Spruelike Enteropathy Associated With Olmesartan" by Rubio-Tapia, Murray, et al, was marked for identification.)

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- - -
BY MR. PARKER:
Q. Let's move on to Exhibit No. 8, which is the Mayo Clinic 2012 paper. And I'd like you to turn, please, to -- well, first, we had a discussion before about resolution who are not on steroids. You recall that?
A. I do and I recall pointing out the difference between improvement and resolution.
Q. Right. And just see if we can agree on our reading of what is said here. If you would turn to page 735 --
A. Okay.
Q. -- in the section labeled "Treatment and Subsequent Course," the authors write: Most of the patients in our study had undergone several therapeutic trials without apparent clinical benefit before referral to Mayo Clinic, including the use of gluten-free diet for months, systemic corticosteroids and/or budesonide, N equals 20.

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So 20 of the 22 patients had been given that steroid and had not had, in their words, any apparent clinical benefit?
A. I agree with that, yeah.
Q. We had just discussed that. So I wanted to give you my reference. That's all.
A. Okay.
Q. Now would you please turn to table 3 on the last page?
A. Okay.
Q. Actually, second to the last page --
A. I would, by the way -- clinical benefit, I would like to -- if I had them here to question, I'd like to know exactly what they meant by clinical benefit. That's a bit vague.
Q. Well, and so is improvement. So what is clinical improvement, sir?
A. Clinical improvement would depend on what the presenting problem was.

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Q. Okay.
A. If it is someone with diarrhea and weight loss, improvement would be less diarrhea. At the least -- the least improvement would be a slowing of the rate of weight loss. Better would be less -- would be weight stabilization and best would be weight gain.
Q. One term that we have talked about, but I didn't ask you to define at the outset, was diarrhea. What's a medical -- your working medical definition of diarrhea?
A. That's funny. It's a term that we learn in first year of med school and then no one asks you to define again. Frequent, watery stool.
Q. What is considered to be a normal number of bowel movements a day?
A. There is a standard that I've seen in the literature. I don't remember offhand.
Q. What is your understanding or how you -- well, strike that.

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Do you ever use the term "chronic diarrhea"?
A. Yes.
Q. What does chronic diarrhea mean?
A. Chronic diarrhea is diarrhea that lasts more frequently than not for a month or more.
Q. Okay. With those definitions in mind then, let's turn to table number 3.
A. Table 3, sure.
Q. And here we see the folks at the Mayo Clinic who first report -- well, let me ask you, this was the group that first reported this enteropathy that's associated with -- that was associated with olmesartan in this paper.
A. The same group did make reference to this. They made a vague reference to it in an earlier paper which was on collagenous sprue, if I remember correctly, where they mentioned that a fairly significant number of the

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collagenous sprue patients were taking olmesartan. But if I recall, they didn't draw any direct conclusions. It was sort of a passing observation; whereas, this paper really establishes the case -- the clinical characteristics.
Q. And you were a resident in 2010 when that paper came out. Right?
A. Yes.
Q. At Columbia.
A. Yes.
Q. And to your knowledge, neither you nor anybody else at Columbia drew the conclusion that when they described the six or so patients in that paper on collagenous sprue, that they were describing a different and new clinical syndrome.
A. Well, I can -- I certainly did not and no one else voiced that to me that I recall.
Q. Fair enough. Okay. Now let's go back to table number 3.
A. Sure.

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Q. Are you in agreement with the folks at the Mayo that what they list here are the clinical features of sprue-like enteropathy associated with olmesartan?
MR. SLATER: Objection; foundation.
You can answer.
THE WITNESS: I believe that they're listing the most common or most -- the features that struck them mostly in their original series of 22 patients.
BY MR. PARKER:
Q. My question is, do you agree with it?
MR. SLATER: Objection.
You can answer.
THE WITNESS: Okay.
I think these are some, but not all, of the features.
BY MR. PARKER:
Q. And what other features would you put in such a table listing the

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clinical features of sprue-like enteropathy associated with olmesartan?
MR. SLATER: Objection.
You can answer. It's asked and answered, but you can answer.
THE WITNESS: Well, I think I would actually voice a number of points of contention with this, so we can start with -- let's just go down the list -- gastrointestinal symptoms (e.g. chronic diarrhea, weight loss, and steatorrhea), I agree particularly with the fact that it's labeled e.g., so those are some examples. Those are not every example.
I would also mention that we've seen patients with nausea and vomiting. We've seen patients with pain, abdominal pain. We've seen patients with fatigue. There are case reports with bowel perforation. There are case reports with neurologic deficits,

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certainly dehydration, kidney damage.

And so I've just listed some additional examples for the e.g. part. I'm not even -- I wouldn't swear that I've listed every possible symptom, but I listed some that I'm familiar with.

BY MR. PARKER:

Q. And those symptoms you are telling me are not just symptoms that happen to appear in patients, but are, in fact, symptoms that are characteristic of enteropathy associated with olmesartan.

A. Yes, in my opinion.

Q. I mean, for example, Doctor, someone could have an enteropathy and happen to have cancer also and if -- they could have cancer of the bowel, but you're not going to tell me cancer of the bowel is a feature of sprue-like enteropathy, are you?

MR. SLATER: Objection.

You can answer.

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THE WITNESS: If I felt that cancer of the bowel was more common in patients on olmesartan, which I don't, I have no reason to think that, but if I thought that, then I would list it as a possible feature.

But in the real world, no, I don't think that there is a cancer association.

BY MR. PARKER:

Q. Let's continue on the chart then. What else do you have issue with?

A. I think that this chart is very appropriate for when we're first learning about a disease. I think in clinical practice now, the only one of these that I think is really paramount is evidence of clinical improvement after suspension of olmesartan.

Histologic improvement, I would not -- I would not demand that. That involves an additional invasive procedure for a patient. I don't think

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that that's necessary.

Celiac disease testing, there are two points here that -- well, really three points -- that relate to celiac disease testing. I think it's good to know. I think it's reasonable to do in any patient that you're suspecting olmesartan-associated enteropathy, but I don't think it's required for the diagnosis.

And, furthermore, the biopsy findings are characteristic, but I don't think that they are absolutely required for the diagnosis.

Q. So my questions have been are there any other clinical features as outlined here with which you agree -- disagree, and I know you've given me a full answer. I'm not going back over the gastrointestinal symptoms.

A. Okay.

Q. Are there any other clinical features as outlined here that you disagree with and say this is not part of

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this syndrome or you need to add to? That's what I'm not hearing.

A. Because most of these are negative findings. They're saying exclude this, that, and the other, negative IgA/tTG antibody test --

Q. Is that required?

A. No, not in my opinion.

Q. So you don't have to rule that out.

A. No.

Q. Okay. Do you have to rule out lack of a clinical response to gluten?

A. No.

Q. Do you have to rule out other causes of enteropathy before you diagnose someone with sprue-like enteropathy associated with olmesartan?

A. No.

Q. And if I understood your last answer, the only thing that you absolutely require for the diagnosis is some clinical report of some improvement

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in one or more of the symptoms.
A. That's the key feature. I would -- if I may --
Q. Sure.
A. -- I'm not saying none of these things add to the picture or none of these things are helpful or none of these things are rational to do. I think they're all perfectly rational to do.
But I think that if a patient had a symptom that a trained gastroenterologist thought might be related to their olmesartan and the gastroenterologist told the patient to get off the olmesartan and they did and they improved, I don't think it would be unreasonable at all for that gastroenterologist to presume or to conclude, I should say, that the olmesartan was the cause of their injury.
Q. And your statement presupposes, does it not, that there are not other confounding treatments going on with that patient, such as drugs being

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given that either are known to induce diarrhea or drugs that are being given that are designed to stop diarrhea?
MR. SLATER: Objection.
You can answer.
THE WITNESS: There are a lot of suppositions in what I just said to you, including, I'll say again, that all of these things are reasonable and rational things to do. We're talking about the absolute requirement.
I think if a patient came in with complaints that were associated with -- that could be associated with olmesartan and enteropathy and the gastroenterologist did nothing except stop olmesartan, didn't do any of these things, it's likely that they would -- they would have a decent chance of being wrong, the patient might have celiac disease. If they didn't do these

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tests, they could miss a case of actual celiac disease, absolutely.
So it's not what I would describe as -- there's a difference between what's ideal and what's reasonable, and there are different discussions that could happen around either of those.
MR. PARKER: Or the standard of care.
MR. SLATER: Objection.
THE WITNESS: As it's developing.
BY MR. PARKER:
Q. Doctor, you made the statement in your report -- I'll refer to page 5 of your report, and that report is Exhibit No. 3 -- that the folks at the Mayo Clinic, to use your words, were necessarily conservative -- that's your word.
A. Okay.
Q. -- when they wrote in their

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paper that the evidence that they had amassed was not proof of causation.
Do you recall that -- or do you see it in your report? Page 5, two-thirds of the way down.
A. Yep. Yeah, and --
Q. What's the basis for your statement, sir -- I just wanted to have you directed to that -- what's the basis for your statement that these authors, when they wrote that their evidence did not prove causality, that they were being, quote, necessarily conservative?
A. Well, this was the first major description of an association between olmesartan and enteropathy. So as we discussed before, associations can be spurious or they can be causative and I think when you have just one case series, you know, there were not a hundred different cases in the literature at this point, the strength of causality was not -- the association was not as well characterized as it is now.

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And I would go on that even though they were conservative, they did go on to state that the association is not likely to be due to chance and I agree with that, also. And I think that since then, the additional literature and my own clinical experience have led me to believe that this is not a chance association, but a causative association.

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(Deposition Exhibit No. Lagana-9, 2016 Editorial "Sprue-Like Enteropathy Associated With Olmesartan: A New Kid on the Enteropathy Block" by Hujoel and Rubio-Tapia, was marked for identification.)

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BY MR. PARKER:

Q. Let me move on to Exhibit No. 9, which is the most -- well, a recent, 2016, paper by, at least, the lead author of the 2012 paper.

MR. SLATER: You mean the

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first listed author?

MR. PARKER: Actually, it's the second listed author, was the lead author of the 2012 paper.

MR. SLATER: First listed author.

MR. PARKER: First listed author.

MR. SLATER: "Lead" is somewhat ambiguous to me.

MR. PARKER: I see. Okay.

BY MR. PARKER:

Q. Doctor, are you familiar with this paper?

A. It doesn't ring an immediate bell. Is it in my reliance list?

Q. It is not in your report. That, I can assure you.

A. Okay.

Q. And I don't see it in your supplemental reliance list either.

A. Okay. It doesn't look familiar.

Q. Okay. Well, then, I'll just

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ask you this question: If you could turn to the third page of this report --

A. Third page -- page 63?

Q. Yes. I'm sorry.

A. Okay.

Q. -- do you see the box -- this appears to be -- well, at the bottom of figure 1, it says, "Proposed management for patients with sprue-like enteropathy associated with olmesartan"?

A. Uh-hum.

Q. Can I call this an algorithm?

A. Uh-hum.

Q. That would be yes, Doctor?

A. Oh, yes. Sorry.

Q. Okay.

A. A proposed algorithm.

Q. A proposed algorithm. And that was my next question: This is now 2016, four years after the report we just got done looking at. Do you agree with the box that's labeled supporting evidence for this syndrome?

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MR. SLATER: Objection. You can answer.

THE WITNESS: Well, I would certainly agree that all of these are potential supportive pieces of evidence. I would not necessarily say that every one of these is necessary to make the diagnosis.

BY MR. PARKER:

Q. Please turn to the first page of this paper.

A. Okay.

Q. On the bottom of the first -- on the left side of the page, they write, "Confirmation of diagnosis requires clinical resolution of symptoms after olmesartan withdrawal."

Do you agree with that?

A. I think resolution is -- I don't agree with that, because I think resolution is too strong a statement.

Q. Have you published papers in which you state that after you stop olmesartan, you have resolution of

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symptoms?
A. Well, certainly in many cases, you do. I don't recall if I've specifically put that in a paper. I might have.
Q. So we go back to -- I'm not sure I ever got an answer to my question what constitutes improvement. If someone has reported diarrhea with ten bowel movements, or what we see in the papers, evacuations -- I love that --
A. Yes.
Q. -- per day and it goes down to eight after olmesartan is withdrawn and stays at eight, is that sufficient clinical improvement to justify a diagnosis of sprue-like enteropathy?
MR. SLATER: Objection.
You can answer.
THE WITNESS: I think that's too much -- it's too much of a vacuum. You know, you're describing just one factor in a patient's care that I would -- I

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would really want to know more about the full clinical picture of the patient before I said whether two less bowel movements is an improvement or not.
BY MR. PARKER:
Q. So then help me understand, as a pathologist, what you would expect and demand to determine whether some degree of improvement is enough to constitute dechallenge.
MR. SLATER: Objection.
You can answer.
THE WITNESS: Well, so you used an interesting phrase there, which is as a pathologist. What we're talking about with number of stools per day, the improvement there would really be a determination that a gastroenterologist would make, not a pathologist.
So I have seen before and after biopsies and I can comment

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quite specifically on what I've seen in the dechallenge biopsies and what led me to believe that there was a positive dechallenge.
How many stools per day difference, that's more of a question for a gastroenterologist, I think.
BY MR. PARKER:
Q. Fair enough. In the context of your world of pathology, what do you demand to see pathologically in terms of improvement, not resolution, but improvement, before you are prepared to say, this shows dechallenge from the cessation of olmesartan?
A. Okay.
MR. SLATER: Objection.
You can answer.
THE WITNESS: Okay. Assuming that I have a pre -- an on-olmesartan biopsy and assuming that we're talking about the small intestine --

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MR. PARKER: We are.
THE WITNESS: Okay -- then what I'd like to see is lengthening of the villi, longer villi than what were there before. I would like to see less inflammation, be it in the lamina propria or in the epithelium. I would like to see less subepithelial fibrosis. I would like to see less crypt apoptosis. I would like to see fewer neutrophils and eosinophils and potentially shorter crypts, and so those are most everything that can happen histologically.
So I would look at all of those factors and if there was an improvement in one or more of those, I would consider that evidence of dechallenge. And the more improvements that there were, the stronger I would see the evidence.

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BY MR. PARKER:
Q. Well, maybe that answers my next question. I'm not sure.
A. Okay.
Q. Can you quantify terms like -- I wrote down more, less, less. Can you be any more quantitative as to what you demand in each of those pathologic findings?
A. Yeah, it depends a lot on the findings, but we can go through them. So the villous architecture, a normal villous should be four or five times taller than a crypt is deep.
So, you know, if -- if at baseline there's a little tiny nub of a villous and a big crypt, instead of being five times taller, it's one-fifth the size. So I can look at that ratio and see is the ratio improving or not.
So that's how I would assess improvement in the architecture of the villi.
Q. And that's what I'm trying

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to press you on, Doctor. If that 1 to 5 ratio goes 1.5 to 5, is that improvement such that you would say, oh, that's dechallenge?
MR. SLATER: Objection.
You can answer.
THE WITNESS: I would say that that degree of change would be very difficult for me to confidently state is -- on its own is evidence.
So in that case then, I would look to other factors like we -- that we discussed, such as intraepithelial lymphocytosis, so I would ask was there intraepithelial lymphocytosis at the initial presentation and if there was, well, I could count how many intraepithelial lymphocytes there are in the most concentrated areas and then I could compare that to the post -- to the -- to the dechallenge.

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BY MR. PARKER:
Q. And is normal 40 per hundred?
A. No, that's abnormal. That's what a lot of people use as a threshold for celiac disease, 30 to 40 --
Q. I thought that was a cut line, so I'm wrong about that.
A. 20 -- well, different parts of the small intestine have different cutoffs. In the ileum, which is the most distal part of the small intestine, up to 40 can be allowed because it's a very immunologically active part of the small bowel --
Q. Let's talk about the duodenum.
A. Yeah, in the duodenum, 20 is generally considered normal, 20 per 100 enterocytes.
Q. So if you had someone who had 30 lymphocytes in the epithelial tissues and it went down to 25, is that degree of -- of improvement sufficient to

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say that's dechallenge?
A. Again, these -- these are small, difficult to appreciate changes. I would have to look at the whole picture.
If the villi were a little better, if the lymphocytes were a little less, the lamina propria inflammation was a little bit improved, the crypt apoptotic bodies were a little less frequent -- you know, if all of these subtleties -- one of those subtle alterations, I don't think I would conclude it was a convincing dechallenge.
If I had all of them, even if they were just small, subtle variations, I would probably suggest that there had been some clinical improvement.
Q. Let's talk about a different aspect of this.
A. Sure.
Q. What is the time course after drug cessation that -- beyond which you would say that can't be attributed to

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drug withdrawal?
A. We're talking about histology now or clinical?
Q. Yes. I'm staying in histology.
MR. SLATER: Objection.
You can answer.
THE WITNESS: I think this is an area that's still being investigated, so I am happy to analogize a little bit to celiac disease. In adults with celiac disease, I think several months, three to six months, to see an appreciable improvement in the histology is fairly normal and there are patients who take about a year. I've seen patients improve in three to six months in olmesartan enteropathy.
I don't recall seeing patients without any histologic improvement in over a year, but that's -- I don't recall seeing

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it. That's not saying it doesn't happen.
There is in celiac disease the refractory state, which has not -- no analogous disease has been identified in olmesartan yet, like refractory olmesartan enteropathy, but it's possible.
BY MR. PARKER:
Q. So going back to my original question about olmesartan, you said it's still being worked out or words to that effect.
A. Uh-hum.
Q. Is there currently no outside time limit that -- after which you will reject the notion of there being dechallenge?
MR. SLATER: Objection.
You can answer.
THE WITNESS: Well, I think that -- I would say that most patients who have been biopsied post dechallenge have improved

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within about six months to a year. I couldn't really, though, exclude any time period.
Now if you had said 25 years, would I agree that that's extremely unlikely, I would, but --
BY MR. PARKER:
Q. So if dechallenge is the sinequan nom of giving a diagnosis, someone would have to wait a year or more to get a diagnosis?
MR. SLATER: Objection.
MR. PARKER: Is that what I understand you to say?
THE WITNESS: Well, there are two different -- we're talking about clinical and histologic --
MR. PARKER: I'm staying on histologic, that's correct. For you to buy into the notion that there has been a proper diagnosis of sprue-like enteropathy, you're saying you're not going to --

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you're not going to buy into that until you see some pathologic evidence of improvement; correct?
MR. SLATER: Objection.
You can answer.
THE WITNESS: No, I don't believe I said that. I think I said that there had to be a clinical improvement following -- I didn't put a pathologic improvement as an absolute necessity to make the diagnosis.
BY MR. PARKER:
Q. Okay. So as long as there's clinical improvement, even though there's no pathologic improvement, you're okay with doctors putting the diagnosis of sprue-like enteropathy on someone; correct?
A. If there's clinical improvement, but there's no pathologic improvement, you're saying.
Q. Yes, sir.
A. I would consider it an

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exceptional case and I would consider it, from my end, the diagnosis to be somewhat uncertain. But I would not -- if an experienced gastroenterologist thought that was the diagnosis and I had no better diagnosis, I wouldn't fight with him on it.

Q. And, Doctor, is it within your area of expertise -- if not, I'll move on -- to discuss now with me what degree of clinical improvement would be needed before someone can conclude there's been successful dechallenge?

MR. SLATER: Objection.

You can answer.

MR. PARKER: In the context of sprue-like enteropathy.

THE WITNESS: I think it's a better question for a gastroenterologist.

BY MR. PARKER:

Q. Let's turn now to rechallenge. Doctor, is there a period in which someone has to return to

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baseline before they're rechallenged to any type of a drug before you can say there's been a successful rechallenge?

MR. SLATER: Objection.

You can answer.

THE WITNESS: Return to baseline meaning their normal state of health?

MR. PARKER: Normal state of health, yes, sir.

THE WITNESS: I don't think that you need to require anyone to return to their normal state of health before you can say that there's been a successful dechallenge.

BY MR. PARKER:

Q. So if a drug, any drug, is suspected of causing an enteropathy and while it is still in someone's system and you restart that drug and that person has symptoms again, you would call that a successful rechallenge?

MR. SLATER: Objection.

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You can answer.

THE WITNESS: If the drug is still within someone's -- so there's been no dechallenge.

MR. PARKER: No, let me start again. My question wasn't clear.

BY MR. PARKER:

Q. You understand the concept, I'm sure, of half-life of drugs?

A. I do.

Q. Do you know the half-life of olmesartan?

A. I believe it's about 13 hours.

Q. And do you know how many days would have to elapse before all the metabolites or the parent compound were out of one's body?

A. There's a calculation that can be done. I haven't done it.

Q. It would be a number of days, we can agree upon that --

A. I would.

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Q. -- if 13 hours is the half-life? Okay. And what you're telling me, Doctor, is, if you resumed olmesartan within the period of time in which half-life has not expired -- with me so far?

A. Yes.

Q. Okay -- and symptoms resumed, you would say that that's a successful rechallenge?

MR. SLATER: Objection.

You can answer.

THE WITNESS: That's a pretty vague question. It could encompass a lot of clinical scenarios. If a patient stopped olmesartan for several days, was feeling better, having a clinical response, and then restarted olmesartan and immediately felt worse, I could accept that as a dechallenge/rechallenge.

BY MR. PARKER:

Q. So going back to my example

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-- and if you're not comfortable because we're dealing with clinics, then you -- clinical questions -- if someone comes in and says, Doc, you know, I got ten bowel movements a day, I got this terrible diarrhea, I've had it for a number of days, and the doctor says stop your olmesartan. After three days, it goes down to seven bowel movements. Patient goes back on olmesartan, it goes back up to ten, is that in your opinion successful dechallenge and rechallenge?

MR. SLATER: Objection again.

You can answer.

THE WITNESS: Well, it's really -- it would be a clinical judgment on the part of the gastroenterologist. If you want me to opine on it, I can, but --

MR. PARKER: No. I'm asking you to opine on it only if you have a considered expert opinion. If you're speculating and you want

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to punt to a GI, that's perfectly fine with me, also.

THE WITNESS: All right.

MR. SLATER: Objection to the whole entire lead-in on that.

You can answer.

THE WITNESS: I'm happy to punt that to a GI.

MR. PARKER: All right. Good. We'll talk to someone else.

BY MR. PARKER:

Q. Doctor, I want to pursue this discussion, but using a different substrate, gluten.

A. Okay.

Q. Again, as always, if this is outside your area of expertise, tell me and I'll move on.

A. Sure.

Q. When someone who is worked up and is thought by clinicians and pathologists such as yourself to have celiac disease, and the clinician says go on a gluten-free diet, understanding

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there's variability in the world, Doctor, what is the expected period of time in which you would expect to see clinical improvement?

MR. SLATER: Objection.

You can answer.

THE WITNESS: Clinical improvement, not histological improvement?

MR. PARKER: We're going to go clinical first.

THE WITNESS: Weeks.

MR. PARKER: Weeks. Okay.

BY MR. PARKER:

Q. And if the person has been on a gluten-free diet then for months with no clinical improvement, would you say that was a failed dechallenge?

MR. SLATER: Objection.

You can answer.

THE WITNESS: I would say that it becomes less likely, but I wouldn't necessarily say it failed. I would want to know more

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about the patient.

If they had a negative celiac genotype and they had never had celiac antibodies, then I would say you're wasting your time, move on.

If the patient had otherwise fairly typical symptoms of -- or presentation of celiac disease, I would not be -- and I was asked my opinion, because I would not be the one making this decision, I would not be satisfied that the gluten dechallenge had failed.

BY MR. PARKER:

Q. Let's turn to histopathology.

A. Okay.

Q. In a patient with a diagnosis of celiac disease who goes on a gluten-free diet, what's the time course when one is on a gluten-free diet that you would expect to see histologic improvement?

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MR. SLATER: Objection.
You can answer.
THE WITNESS: Months would be standard.
BY MR. PARKER:
Q. And when you say months, you mean, I wouldn't necessarily expect any improvement until months have gone by --
A. Right.
Q. -- on the diet?
A. Right. I wouldn't -- not that you can't see it. You can see it, but I wouldn't necessarily expect it until a few months had passed.
Q. Are you familiar with randomized clinical trials referred to as N-of-1 trials?
A. Randomized clinical trial -- I've heard of N-of-1. I'm not sure I understand N-of-1 in the context of an RCT.
Q. In terms of -- let me -- are you familiar with the method of doing a clinical trial in one patient where that

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patient is blinded and the physician is blinded to whether they're taking drug or placebo?
A. I don't think that I'm terribly familiar with that. At Columbia, we do have an N-of-1 program where patients with various cancers can have their tumors implanted in an animal model and the tumors are grown in the animal model and various therapeutics are tried.
So N-of-1 certainly means something -- some neurons fire when you say that, but what you just described is not the situation that I'm totally familiar with.
Q. Okay. Then I'll move on.
A. Okay.
Q. Let's talk about your report.
A. Can we do five minutes before we do that?
MR. SLATER: Yeah, sure.
MR. PARKER: I'm going to

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keep my word, whenever you want a break. I was almost into a question, but I haven't quite gotten there.
THE WITNESS: I'm afraid I consume quite a bit of liquids throughout the day, so I'll be right back.
(A recess was taken from 2:27 p.m. to 2:40 p.m.)
BY MR. PARKER:
Q. Before the break, Doctor, I had asked you to pull out your report. I hope you have that in front of you at this point.
A. I do.
Q. Now, without repeating, but just setting the framework for my next series of questions, Doctor, if I recall our discussion earlier, at the time Mr. Slater asked you to write this report, you had already formed your opinion on general causation for the reasons that you described earlier.

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A. I had formed the bulk of my opinion before I spoke to Mr. Slater.
Q. Okay.
And, Doctor, you make reference to, in here -- let me see if I can find it -- I think it's elsewhere, but I see it in the last section, 4, under opinions, on the last page, page 8 --
A. Okay.
Q. -- you make reference to applying the scientifically accepted methods set forth above.
Can you describe for me what methods you have in mind that you discussed in this report by which or through which you reached an opinion on general causation?
A. Well, I think the scientifically accepted method for any physician to stay abreast of new developments in medicine is to review the peer-reviewed, published literature, which I've done, to apply one's own

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experiences with various entities, which I've done, to discuss new entities with your colleagues and experts, which I've done, and I would say that those are the scientifically accepted methods which I have employed.

Q. We can agree that in the report itself, there's no discussion of any of the literature reporting on epidemiological studies; correct?

A. Let's double-check.

Q. Sure.

(Pause.)

THE WITNESS: I believe -- we can clarify this if necessary -- I believe that the Theophile article, number 23, and the Marthey article, get into epidemiology; but the epidemiologic article that I consider most important is the Basson article, which I did not reference.

MR. PARKER: My question I

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don't believe was did you reference anything. My question is, did you have a discussion of that in your report.

THE WITNESS: Ah, okay. I'm going to take another look.

MR. PARKER: Please.

(Pause.)

THE WITNESS: I would say a passing reference was made to the question of epidemiology where I -- on page 7, I talk about how Marthey, et al conducted a survey of French gastroenterologists and discovered 36 cases, which one can make an inference about the epidemiology of olmesartan enteropathy in France on the basis of that article.

But I would agree that major emphasis to epidemiology is not present in my report.

BY MR. PARKER:

Q. Are you telling me, sir,

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that the Marthey paper where they report the results of a survey is an epidemiological study?

A. I'd have to -- I'd have to look at it again. I would be happy to look at it again if you want to wait.

Q. Well, why don't you take a look at your description of the Marthey study on page 7, see if that helps first, of your report.

A. Well, I did just read that. I would agree with you that epidemiology is not an important part of the document that I produced, the written document.

Q. And I agree with that -- I mean, I accept that.

A. Okay.

Q. My question is, you're not describing Marthey as an epidemiological study, are you?

A. Let me double-check it.

Q. Please.

(Pause.)

THE WITNESS: Not in the

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classic sense. It overlaps with epidemiology, of course, if you survey a population of -- of gastroenterologists, but it's not by any means a classic epidemiology study.

BY MR. PARKER:

Q. There are no controls in the study at all; correct?

A. Correct.

Q. And that is one of the essential tools in epidemiological research, is it not?

A. It is.

Q. Okay.

Doctor, do you adhere to the practice of evidence-based medicine?

MR. SLATER: Objection.

You can answer.

THE WITNESS: Of course. I believe everyone does these days.

BY MR. PARKER:

Q. Some do not, trust me.

A. Fair enough.

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Q. Tell me what that phrase means to you, Doctor.
A. Well, evidence-based medicine means that we base our decision making, our diagnostic algorithms, our treatment algorithms on the basis of the published literature and scientific studies and not on, say, you know, expert opinion or things of that sort.
Q. Doctor, it is not uncommon when scientists publish in the peer-reviewed literature, particularly in a good journal, that you're required by the editors to disclose the limitations of one's study?
A. Yeah, I think that's common.
Q. You said at the outset of the deposition, you approached this task as a scientist would, looking at evidence on both sides of the issue; correct?
A. Yes.
Q. Explain for me, as you looked at the evidence in the course of preparing this report, what did you

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consider to be the strongest reliable evidence arguing against your position of general causation?
MR. SLATER: Are you going to pay him a fee for that?
MR. PARKER: I've already made you -- well, I've made him money. He's going to bill you some more.
THE WITNESS: Give me a minute to look through the list.
MR. PARKER: Please, please. Take your time.
MR. SLATER: Don't think too hard. No, I'm just kidding.
(Pause.)
THE WITNESS: Well, I really came across nothing that made me think, maybe this association is spurious, maybe it's not causative. I didn't have that opinion based on anything that I read. I believe firmly that this is causative in some patients.

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If -- I would say that before I did some of the reading, such as ROADMAP, Padwal -- I think those two in particular -- they make me think that this is probably a pretty uncommon event for patients, but uncommon and nonexistent are two very different things.
So I am firm that this -- that this association is real and causative. I think considering these two studies, particularly ROADMAP, didn't find a real signal for enteropathy probably means that because they -- that they were underpowered to detect what I believe to be an uncommon event.
BY MR. PARKER:
Q. I'm waiting -- I wasn't sure whether you were finished with your answer.
A. That's it.
Q. So if I can understand, my

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question was phrased in terms of what did you find to be the strongest evidence that was inconsistent with your opinion, not that it persuaded you, on general causation; and I think your answer is, Padwal and the ROADMAP study. But if I'm wrong, you correct me.
MR. SLATER: Objection.
You can answer.
THE WITNESS: Can you repeat again the question that you wanted me to answer?
MR. PARKER: Sure.
BY MR. PARKER:
Q. The question I want you to answer is, what evidence, if any, as you reviewed the literature did you find presented the best evidence that was inconsistent with your general causation opinion.
A. Okay.
MR. SLATER: Objection; asked and answered.
You can answer.

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THE WITNESS: I don't think anything was really inconsistent with my opinion.

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(Deposition Exhibit No. Lagana-10, 2016 Article "Olmesartan-associated sprue-like enteropathy: a systematic review with emphasis on histopathology" by Burbure, Lagana, et al, was marked for identification.)

- - -

BY MR. PARKER:

Q. Let's turn now to Exhibit No. 10, which is your 2016 paper --

A. Sure.

Q. -- with colleagues. Do you have it, Doctor?

A. I do.

Q. For the record, this is the paper that you published with others. You are the last author in this paper; correct?

A. Correct.

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Q. All right.

And I think you describe this in your report as one in which you were the senior author.

A. Yes.

Q. Certainly not senior to Peter Green, but certainly -- well, let me ask you, in all seriousness, what does that mean to say that you're the senior author on this paper?

A. It means that the concept of this particular paper was mine and that I guided the project from beginning to completion.

Q. What does it mean -- the title of your paper is "Olmesartan-associated sprue-like enteropathy: a systematic review with emphasis on histopathology."

What does it mean to do a systematic review?

A. Systematic review means that we attempted to address all the published literature on this topic in this paper.

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Q. In an unbiased, scientific sort of a way?

A. Yeah. I certainly didn't go into it with bias -- with any cognitive biases I was aware of anyway.

Q. I'm asking, was part of your intent in writing this paper to convince others that olmesartan was, in fact, causing sprue-like enteropathy?

A. No, that really -- the reason why I wanted to write this paper was really to discuss the histologic differential diagnosis and to talk about the pathology of it.

Convincing others that this existed was not really a big part of my thinking when I was putting this together.

Q. Let's go through some of the things you say in this paper. If we look just at the summary -- and I'm going to say "you," but this was a collaborative effort; correct?

A. Yeah.

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Q. Okay -- were you the primary author?

A. Meaning did I write most of what is here?

Q. Did you write the -- at least the first draft of this?

A. I wrote a fair amount of this. I didn't write all of this. It would be tough now for me to remember exactly what phrases or paragraphs I wrote and what phrases or paragraphs someone else wrote.

Q. And I'm not going to ask you that question, but --

A. Okay. I wrote some of it.

Q. Okay. And other than yourself, was there one or others of here who were what you would describe as major contributing authors of the piece?

A. How would you define major contributor?

Q. Did some original drafting of certain sections of the paper as opposed to simply reviewing and offering

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editorial suggestions.
A. Dr. Burbure, who was the first author on the paper, did a fair bit of the writing.
Q. Anyone else, sir? Other than yourself obviously.
A. I would say the two of us did the vast majority of the -- of the drafting of verbiage.
Q. So let's turn then to the summary. You wrote, "It is not well established if other ARBs cause such a syndrome, although case reports suggest that it can"; correct?
A. Yes.
Q. And we will talk a little bit later about your discussion of those, but how do the case reports of the A -- of the other ARBs differ from olmesartan other than the number of them?
A. Sorry. I'm -- one of my friends always says, "If my aunt had different anatomy, she'd be my uncle."
But, anyway, the number of

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them happens to be I think a very important piece here. That's how they differ. There's --
Q. That's fine.
A. -- just a couple as compared to over a hundred.
Q. There are no trick questions yet. Okay.
So other than the number, there's no other substantive difference in the case reports of other ARBs and enteropathy versus olmesartan. Are we in agreement?
A. Of the case reports I've read of other ARBs causing enteropathy, I would say that they look very similar to olmesartan.
Q. And does the group at Columbia have patients who have gone on other ARBs -- "other" meaning non-olmesartan -- and who have developed an enteropathy after which they improved after discontinuation that have not found a way into the peer-reviewed literature?

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A. To the best of my knowledge, we have a couple of patients like that.
Q. And do you know what drugs they were on?
A. I have vague recollections. I wouldn't -- I couldn't really swear to them in a court of law.
Q. Doctor, what other -- I recall not having asked you this question: What other drugs in your medical training and experience do you accept as causes of enteropathy, putting aside ARBs?
A. Well, one that we see fairly frequently -- well, one that we see occasionally, I should say -- at Columbia is mycophenolate or products derived from mycophenolic acid, which is used as an immunosuppressant drug in patients with organ transplantation. That can occasionally cause similar enteropathic changes which could be morphologically similar to what we see with angiotensin receptor blockers.

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Other drugs that we see -- well, NSAIDs are a common drug. We often see some inflammation of the intestines in patients who are NSAID users.
I would say this particular pattern that -- the patterns that we've seen with -- we don't typically see a sprue-like enteropathy in NSAID users, but it's plausible and probably has come across my desk over the years.
Q. Is the variability as you have described it today in the histopathology in patients using olmesartan replicated with any other drug that you accept as a cause of enteropathy?
A. Let me just rephrase that back to you and make sure I understood it right.
Q. Yeah.
A. Do other drugs which cause enteropathy have as broad a spectrum as olmesartan?
Q. I managed to get the

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question out. You managed to understand it, yes.
A. Okay. Good. Yeah, mycophenolate can have very variable presentation from very, very subtle abnormalities to total villous atrophy, yes.
Q. So if I were to pull out literature on that drug, I would see histologic descriptions of it that would approximate what you've written in papers such as the one we're talking about now regarding olmesartan.
A. Yeah, you could find such descriptions.
Q. Let's go on then. On the summary, you also wrote --
A. Summary on page 1, you mean?
Q. Yes, sir.
A. Okay.
Q. -- there are no guidelines regarding the histopathologic distinctions of olmesartan-associated enteropathy from other causes of sprue,

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and then you give some parenthetical examples; correct?
A. Uh-hum.
Q. And we touched upon this a little bit earlier in the deposition and you stand by this statement.
A. I believe so.
Q. Well, only you know, Doctor.
A. That was the main purpose of this article, was to help pathologists who may be encountering this entity to differentiate it from other entities which may histologically resemble olmesartan enteropathy.
So, yeah, there are no official guidelines anywhere. This is my or our best take on it.
Q. Let's go on to the next page then. At the bottom of the left-hand column, you write, "Clinical symptoms resolved quickly after cessation of the medication in all cases and the histologic changes disappeared in the vast majority (17 of 18)."

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With regard to the one who -- if I'm reading this correctly -- did not have improvement in histology, going back to our earlier discussion, would you say that that person still had dechallenge?
A. Well, so first, this is not my work. This is a reference to another -- to another paper and I believe I'm referencing Rubio-Tapia there, so let me see -- yeah, so referencing Rubio-Tapia, and I believe in the Rubio-Tapia paper -- I believe they all had improvements, but let me just double-check this.
Q. Sure.
A. So they described 17 cases with histologic recovery of the duodenum, 17 of 18, and one case with focal partial villous atrophy, but they don't say what that patient had before, so I couldn't say if there had been some improvement or not in that patient.
Q. Let's go on to numbered page 130. You write on the right-hand column

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-- and you're referring back to a couple cases in the literature -- you write, "These observations are consistent with our experience where patients typically start to notice great improvement just days after medication cessation." Let me stop there.
Does what you wrote here describe the majority of your patients? And when I say "yours," I mean the patients seen at Columbia?
A. I'm sorry. The word you used there was great majority?
Q. Yeah.
A. I couldn't say if it represents the great majority. It certainly represents many patients. In fact, that's how Joe Murray discovered this association in the first place, is patients staying in the hospital who weren't on their olmesartan for even a few days reported to him that they started feeling better.
Q. So I'm not surprised at

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trial, are you able to say that the majority of the patients seen at Columbia who have symptoms of enteropathy and taking olmesartan and are told to stop taking olmesartan have, to use your words, great improvement just days after medication cessation?

A. That would be my understanding based on discussions had at clinicopathologic conferences, interdisciplinary conferences.

But Drs. Green and Lebwohl would be better able to speak to that and both reviewed this paper for accuracy, so --

Q. Let's go on to numbered page 131 -- let's go to page 132.

A. Sure.

Q. You reference here clinical trials of some of the other ARBs, particularly azilsartan. Do you see that?

A. Yep.

Q. Did you review the clinical

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trials of azilsartan medoxomil for purposes of writing this paper?

A. No.

Q. Do you recall who did that?

A. Who referenced the reference 28, you mean?

Q. Who reviewed the clinical trials of azilsartan.

A. You mean who found article 28 and included it in the statement.

Q. And studied it, presumably.

A. I don't.

Q. Okay. Let's go on then.

Down at the bottom of section 5, I think this confirms what you said earlier, but let me just make sure, you wrote: This broadens the differential even further and there is no cardinal finding which can establish the diagnosis of olmesartan-induced injury based on histopathology.

That remains your view today.

MR. SLATER: You didn't read

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it completely accurately, but you can answer.

MR. PARKER: Well, I certainly wanted to, so I'll try it one more time.

MR. SLATER: I know what you wanted to. I know what you desire in life. Just making an objection.

BY MR. PARKER:

Q. "This broadens the differential even further and there is no cardinal finding which can establish the diagnosis of olmesartan-induced injury based solely on histopathology," does that remain your opinion today?

A. It does.

Q. Under celiac disease, section 5.1, the last sentence, "Ultimately, seronegativity and ARB use are the most meaningful discriminators between celiac disease and ARB enteropathy," does that remain your opinion today?

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A. We should have included -- no, I think a response to a dechallenge with -- of ARB is probably more meaningful.

Q. So if you were to rewrite that sentence, how would it be rewritten consistent with your opinions today?

A. I would probably say something to the effect of, ultimately, the history of ARB use with improvement of clinical symptoms following ARB dechallenge is the most meaningful discriminator between celiac disease and ARB enteropathy.

And we could go on. Certainly seronegativity and lack of a response to a gluten-free diet do add further supportive evidence.

Q. Earlier -- just so I'm sure I'm understanding, seronegativity and lack of response to a gluten diet don't rule out celiac disease. Would you agree?

A. Seronegativity and lack of a

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response to a gluten-free diet?
Q. Uh-hum.
A. You would be describing zebras amongst zebras -- sorry. That's sort of medical jargon to say the rarest of the rare. And I'm not sure how you make the diagnosis -- if the person has never had positive celiac antibody testing and has never responded to a gluten-free diet, I'm not sure how you could ever confidently state that they have celiac disease.
Q. My question -- I'm not sure I got an answer to it -- is, in a person who does not have a positive result of the antibodies for celiac disease, seronegativity, and who does not respond to gluten, does that in and of itself, those two factors, rule out celiac disease?
MR. SLATER: Objection. He just answered the question.
You can answer it again.
THE WITNESS: Effectively.

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BY MR. PARKER:
Q. What is refractory celiac disease?
A. Refractory celiac disease is a complication, a very rare complication, of celiac disease, wherein patients stop responding to a gluten-free diet.
Q. And seronegative celiac disease, what is that?
A. That's a celiac disease patient who never had a positive celiac antibody test.
Q. Doctor, moving down to table 2 at the bottom, if you were to write this paper today, would you modify that table 2 in any manner or does this reflect your current opinion of the possible histopathologic differences between ARB enteropathies and other enteropathies?
A. I'll say, first, this is a table. It's meant to provide easy, quick access to some information. It's not meant to be an exhaustive list of

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anything, but let me look at it in more detail and see --
Q. Please.
(Pause.)
THE WITNESS: I think since I've written this paper, I've seen more cases of what I believe to be olmesartan enteropathy that look a little bit more like Crohn's disease than I had seen when I wrote this.
So I might have been -- I might have worded that part a little bit differently.
BY MR. PARKER:
Q. How would you change it today?
A. I would probably add something like a -- like a caveat saying that patchy involvements and granulomas can occasionally be seen in ARB enteropathy.
Q. Doctor, down at the bottom of conclusions you wrote, "The mechanism

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of injury is not well established." Do you stand by that statement today?
A. Well, I think that it's an immune-mediated inflammatory disorder and I think that we've seen that pretty -- pretty consistently in the literature.
I think that there has been some advancement as far as molecular mechanism, be it IL15, but I think that increased CD8+ T cells have been pretty convincingly described in the literature, so I think that we do know it's an immune-mediated inflammatory condition.
Q. So are you saying if you were writing this paper, you would no longer say the mechanism of injury is not well established?
A. I wouldn't use that phraseology today.
Q. How would you phrase it?
A. I would say that the mechanism of injury involves immune-mediated inflammation and may involve cytokine abnormalities including